

### **Amendments to the Claims**

This listing of claims will replace all prior versions and listings of all claims in the application.

Claims 1 -29 (Canceled)

30. (Previously presented) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein structure of a desired target protein, said protein structure comprising:
  - i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and
  - ii) a plurality of variable residue positions;
- (B) altering at least one supersecondary structure parameter value of said protein backbone structure of said protein;
- (C) establishing a group of potential amino acid side chains for a plurality of said variable residue positions of said protein; and
- (D) analyzing the interaction of all or part of each of said potential amino acid side chains from said group with all or part of the remainder of said protein structure to generate a set of optimized proteins sequences.

31. (Currently amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein structure of a desired target protein, said protein structure comprising:
  - i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and
  - ii) a plurality of variable residue positions;
- (B) altering at least one supersecondary structure parameter value of said protein backbone structure;
- (C) classifying each variable residue position as either a core, surface or boundary residue;
- (D) establishing a group of potential amino acid side chains for each of said variable residue positions; and
- (E) analyzing the interaction of all or part of each of said amino acid side chains from said group with all or part of [[of]] said protein structure to generate a set of optimized protein sequences.

Claims 32-52 (Canceled)

53. (Previously presented) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein structure of a desired target protein, said protein structure comprising:
- i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and
  - ii) a plurality of variable residue positions;
- (B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acid side chains;
- (C) establishing a group of potential amino acid side chains for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains; and
- (D) analyzing the interaction of all or part of each of said amino acid side chains from said group with all or part of said protein structure to generate a set of optimized protein sequences.

Claims 54-55 (Canceled)

56. (Previously presented) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein structure of a desired target protein, said protein structure comprising:
- i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and
  - ii) a plurality of variable residue positions;
- (B) altering at least one supersecondary structure parameter value of the protein backbone structure of said protein;
- (C) establishing a group of potential amino acid side chains for a plurality of variable residue positions of said protein, wherein at least one of said amino acid side chains is from a hydrophilic amino acid; and
- (D) analyzing the interaction of all or part of each of said potential amino acid side chains from said group with all or part of said protein structure to generate a set of optimized proteins sequences, wherein said analyzing step includes the use of at least one scoring function.

57. (Previously presented) A method according to claim 56 wherein said amino acid side chains are different.

58. (Previously presented) A method according to claim 56 wherein said amino acid side chains are the same.

59. (Original) A method according to claim 56 wherein said hydrophilic amino acid is selected from the group consisting of serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, and histidine.

60. (Currently amended) A method according to claims 53 and 56-59 further comprising physically generating at least one member of said set of optimized protein sequences and experimentally testing said sequence for a desired function.
61. (Previously presented) A method according to claim 30, 31, or 53 wherein said analyzing step comprises a DEE computation.
62. (Previously presented) A method according to claim 56 wherein said analyzing step further comprises a DEE computation.
63. (Previously presented) A method according to claim 56 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.
64. (Previously presented) A method according to claim 61 or 62 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.
65. (Previously presented) A method according to claim 30, 31, or 53 wherein said analyzing step includes the use of at least one scoring function.
66. (Previously presented) A method according to claim 56 or 65 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.
67. (Previously presented) A method according to claim 65 wherein said analyzing step includes the use of at least two scoring functions.
68. (Previously presented) A method according to claim 65 wherein said analyzing step includes the use of at least three scoring functions.
69. (Previously presented) A method according to claim 65 wherein said analyzing step includes the use of at least four scoring functions.
70. (Previously presented) A method according to claim 66 wherein said scoring function is an atomic solvation scoring function.
71. (Previously presented) A method according to claim 70 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.
72. (Previously presented) A method according to claim 30, 31, 53, or 56 further comprising experimentally testing at least one member of said set.
73. (Previously presented) A method according to claim 63 further comprising the step of:

generating a list of additional optimal sequences from said globally optimal protein sequence.

74. (Previously presented) A method according to claim 73 wherein said generating includes the use of a Monte Carlo search.

75. (Previously presented) A method according to claim 30, 31, 53, or 56 wherein said analyzing step comprises a Monte Carlo computation.

76. (Currently amended) A method according to claim 75 further comprising the step of: testing some or all of said protein sequences from said ~~list~~ set to produce potential energy test results.

77. (Previously presented) A method according to claim 76 further comprising the step of:

analyzing the correspondence between said potential energy test results and theoretical potential energy data.

78. (Previously presented) A method according to claim 30, 31, 53, or 56 further comprising modulating the protein backbone structure.

79. (Previously presented) A method according to claim 30, 31, 53, or 56 wherein said variable residue positions comprise one or more non-core positions.

80. (Currently Amended) ~~A method according to 53 wherein step (c) further comprises a second group for a second variable position has a second set of at least two amino acid side chains. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:~~

(A) receiving a protein structure of a desired target protein, said protein structure comprising:

i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and

ii) a plurality of variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acid side chains;

(C) establishing a group of potential amino acid side chains for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains and a second group for a second variable position having a second set of at least two amino acid side chains; and

(D) analyzing the interaction of all or part of each of said amino acid side chains from said group with all or part of said protein structure to generate a set of optimized protein sequences.

81. (Currently amended) A method according to claim 80 wherein said first and second sets of amino acid side chains are different.

82. (Currently amended) A method according to claim 80 wherein said first and second sets of amino acid side chains are the same.

83. (Previously presented) A method according to 30, 31, 53 or 56, wherein said at least one non-variable residues is fixed.

84. (Previously presented) A method according to 30, 31, 53 or 56, wherein said at least one non-variable residues is floated.

85. (Previously presented) A method according to claim 30, 31, 53 or 56 wherein said variable residue positions are structurally functional residue positions.

86. (Previously presented) A method according to claim 30, 31, 53, or 56 wherein said variable residue positions are biologically functional residue positions.